PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Elizabeth M. JAFFEE et al.	Atty. Dkt. No.: 001107.00363
Application No.: 10/618,088	Confirmation No.: 4098
Filed: July 14, 2003	Art Unit: 1643
For: MESOTHELIN VACCINES AND MODEL SYSTEMS	Examiner: Anne Gussow

DECLARATION UNDER RULE 132

Commissioner of Patents
U.S. Patent and Trademark Office
Customer Service Window
Randolph Building, 401 Dulany Street
Alexandria, VA 22314

Sir:

I, Drew M. Pardoll, M.D., Ph.D., declare:

1. I am the Seraph Professor in the Department of Oncology and Director in the Cancer Immunology Program at Johns Hopkins University School of Medicine, Baltimore, MD.

2. I received a B.S., M.D., and Ph.D. in Molecular Biology from Johns Hopkins University. I was a fellow at the National Institute of Allergy and Infectious Diseases, Bethesda, Maryland.

3. I am aware that the U.S. Patent and Trademark Office has urged that it would have been obvious as of July 14, 2003 to make and use a tumor vaccine of *Listeria monocytogenes* expressing one or more MHC class I-binding epitopes of mesothelin.

4. I do not believe that one of ordinary skill in the art before July 14, 2003 would have believed that such a tumor vaccine would have a reasonable chance of success.
5. Argani et al. (*Clin. Cancer Res. 7*:3862-3868, 2001) identified mesothelin by gene expression analysis as a marker for pancreatic adenocarcinoma. This finding would not have been sufficient to provide a reasonable expectation that mesothelin would be a successful therapeutic target.
6. For example, prostate stem cell antigen (PSCA) is a marker that SAGE data demonstrated was expressed by pancreatic tumors at similar levels to mesothelin. See specification at paragraph [94]. See also Ryu et al., *Cancer Research 62*:819-826 (2002) at Table 3. **Exhibit A.**
7. However, PSCA did not elicit an immune response in the patients who demonstrated a delayed type hypersensitivity (DTH) response to autologous tumor cells after vaccination with an allogeneic GM-CSF-secreting pancreatic tumor vaccine. See specification at paragraph [106] ("We evaluated the lymphocytes from the same 14 patients for the post-vaccination induction of CD8+ T lymphocytes directed against a second overexpressed antigen, PSCA. In contrast to mesothelin, PSCA did not elicit an immune response in the 3 DTH responders."). Mesothelin, however, did elicit such a response; mesothelin-specific T cells were detected in the DTH responders. See specification at paragraph [101] ("Induction of mesothelin-specific T cells was detected twenty-eight days following vaccination in patient 13 a DTH responder, but not in patient 10, a non-DTH responder. Similarly, post-vaccination induction of mesothelin-specific CD8+ T cells was observed in two other disease-free DTH responders (patient 8 and patient 14), but not for two other non-DTH responders

when tested with T2-A2 and T2-A24 cells pulsed with the A2 (FIG. 2B) and A24 (FIG. 2C) binding epitopes, respectively.").

8. Thus, despite similar overexpression of mesothelin and PSCA in pancreatic cancer, the whole-cell, pancreatic cancer vaccine induced no immune response to PSCA. "In fact, PSCA was shown to be overexpressed at higher levels than even mesothelin. However, post-vaccination PSCA specific T cell responses were not detected in the DTH responders and DTH non-responder patients." Specification at [115].
9. The specification explicitly teaches that "overexpression of a protein in a tumor is insufficient to predict the protein's utility as a vaccine target." Specification at paragraph [106], page 39, lines 1-2. At the time of the invention, the reason for the disparate responses to mesothelin and PSCA was unknown and acknowledged as such. See specification at paragraph [115] ("It is unclear at this time why a GM-CSF secreting allogeneic vaccine induces T cell responses to one overexpressed antigen and not to a second similarly overexpressed antigen.").
10. Tumor biology is complex, and abundant expression is not enough to make a marker a good target.
11. Epidermal Growth Factor Receptor is a marker which is overexpressed in colorectal cancers. Cetuximab is an inhibitor of EGFR. However, overexpression of EGFR does not correlate with response to cetuximab in colorectal cancer. See Italiano et al., *Ann. Surg. Oncol. 15,* 649-654 at 650, 2008. Overexpression of EGFR does not correlate with therapeutic response.
12. Despite the elevated expression of EGFR in head and neck squamous cell carcinoma (HNSCC), if a particular mutation (EGFRvIII) is present in the tumors, the efficacy

of cetuximab is abrogated. See Sok et al., *Clin. Cancer. Res. 12:* 5064-5073, at 5068, 2006. Elevated expression alone does not predict therapeutic response.

13. Immunological tolerance would also have prevented one of skill in the art from making any reasonable predictions regarding a vaccine based on overexpression of a marker. See Morris et al., *Clin. Exp. Immunol. 131:* 1-7, 2003. Typically, individuals are immunologically tolerant to normal tissue antigens. See Leitner et al., *Nat Med. 9*:33-9, 2003. The reason for tolerance may be to prevent auto-immune reactions. See Mapara et al., *J. Clin. Oncol. 22,* 1136-1151, at abstract. The ability to overcome immune tolerance was not predictable at the time of the invention. Therefore the successful use of any particular normal tissue antigen such as metholin as an immune target would not have been predictable.
14. For all the above reasons, one of ordinary skill in the relevant art of tumor immunology would not have found that Argani's teaching of overexpression of mesothelin in pancreatic tumors would predictably lead to its successful use as an immune target for pancreatic cancer.

15. All statements made herein of our knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 11/12/09, 2009

Drew M. Pardoll, M.D., Ph.D.